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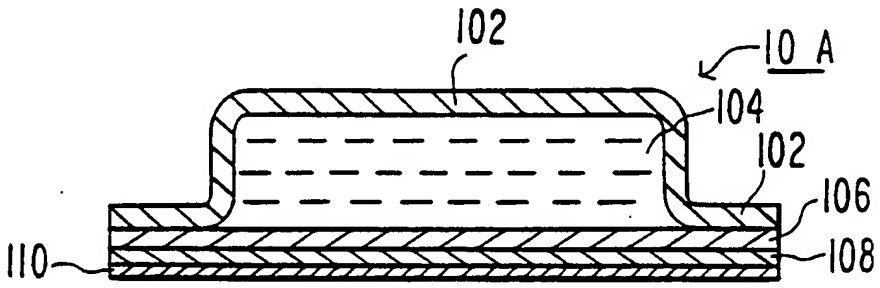

(57) Abstract

The present invention is directed to a transdermal delivery device (10) for the controlled release of a drug or other therapeutic agent to skin or mucosa and adapted to delay the onset of therapeutic agent delivery at a therapeutically effective rate for a predetermined time after placement of the device onto the skin or mucosa. The device comprises a nonaqueous reservoir (104) which contains a therapeutic agent in complexation with an ion-exchange resin and also contains an activating agent, the reservoir having a surface through which the therapeutic agent is released to the skin or mucosa; and a rate-controlling membrane (106) disposed between the skin or mucosa and the releasing surface of the reservoir (104) for controlling the rate at which water is absorbed into the reservoir, the rate-controlling membrane (106) being substantially free of therapeutic agent prior to placement of the device onto the skin or mucosa. The present invention has the additional advantage of providing the therapeutic agent in a stable form prior to placement on the skin or mucosa as well as in a form suitable for absorption after such placement.

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DELAYED ONSET TRANSDERMAL DELIVERY DEVICE

FIELD OF THE INVENTION

The present invention relates to diffusional drug delivery devices, and more particularly to novel methods and compositions for delaying the onset of therapeutic agent delivery for transdermal systems.

BACKGROUND OF THE INVENTION

The transdermal route of parenteral delivery of drugs provides many advantages, and transdermal systems for delivering a wide variety of drugs or other beneficial or therapeutic agents are described in, for example, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,742,951, 3,948,262, 4,031,894, 4,144,317, 4,201,211, 4,286,592, 4,314,557, 4,379,454, and 4,568,343, all of which are incorporated herein by reference.

In these devices, a drug or other active agent is released by diffusion from a reservoir through the agent releasing surface of the device to the skin or mucosa at which the device is applied. Such devices perform well in the administration of many agents but are not suitable for the administration of an agent whose dosage regime requires that the onset of therapeutic effect be delayed for a significant period of time after application of the device at the site of delivery. This is because, in the above devices, the surface through which the agent is released, at the time of application, contains the agent in an amount that is typically at or above saturation and is capable of delivering at a rate that can give rise to therapeutic blood levels. In some cases, the initial rate of release is unacceptably high, and a method for reducing the initial "burst" of agent delivery is described in U.S. Pat. No. 3,923,939. Even in this patent, the agent-releasing surface of the diffusional embodiment contains agent and delivery commences immediately in the manner described above.

One of the advantages of a continuous release dosage form such as a transdermal drug delivery device over oral dosing of medications is the improvement in patient compliance that is obtained from the concurrent removal of one device and application of a new device at

the same time. This advantage is lost when removal and application occur at different times or where onset of a therapeutic effect is desired at an inconvenient time such as shortly prior to awakening from sleep. The devices of this invention are particularly useful over standard transdermal devices in providing a predetermined delayed onset of therapeutic effect for any desired time period after application to the skin. Thus, a device could be removed and a new one applied simultaneously, wherein the desired drug-free interval is still obtained for a period after application.

Additionally, a common problem encountered with transdermal delivery devices is how to deal with unstable active agents. Many agents in their active or otherwise preferred, usually neutral acid or base, form are unstable in transdermal delivery devices. They may be very soluble in most polymer matrices and rate-controlling membranes of transdermal devices, and there are those that tend to degrade the adhesive or other system components. They also usually have a high vapor pressure which requires special concern in packaging. Additionally, storage of the devices "on the shelf" for extended periods prior to use also creates a significant problem for maintaining stability of the active agent itself over an extended period of time. While it is known that many therapeutic agents are stable in the salt form, these agents may be readily absorbable through the skin only in either the free base form, the free acid form or the ester form, for example. In the past, therefore, transdermal delivery devices storing the agent in the form suitable for absorption through the skin could have an undesirably short storage life. Similarly, those storing the agent in a form suitable for storage could have an undesirable low agent delivery rate through skin.

Transdermal delivery devices having agent together with an ion exchange resin for providing storage stability are known. However, these do not provide an initial delay period from the time of placement on the skin to start of delivery of agent from the devices. For example, U.S. Pat. No. 4,692,462 discloses a transdermal drug delivery system having a drug reservoir composed in part of an ion exchange resin. However, the drug reservoir also contains water as well as a hydrophilic polymer gel. The presence of water in the drug

reservoir causes some of the drug to become unbound from the ion-exchange resin and, therefore, immediately available for delivery upon placement of the device on the skin.

There is a continuing need, therefore, for a transdermal therapeutic system that provides a delayed onset of delivery and at the same time provides stability of the drug or therapeutic agent and all components of the device.

SUMMARY OF THE INVENTION

The present invention is directed to a transdermal delivery device for the controlled release of a drug or other therapeutic agent to skin or mucosa and adapted to delay the onset of therapeutic agent delivery at a therapeutically effective rate for a predetermined time after placement of the device onto the skin or mucosa. The device comprises a nonaqueous reservoir which contains a therapeutic agent in complexation with an ion-exchange resin and also contains an activating agent, the reservoir having a surface through which the therapeutic agent is released to the skin or mucosa; and a rate-controlling membrane disposed between the skin or mucosa and the releasing surface of the reservoir for controlling the rate at which water is absorbed into the reservoir and, to a much lesser extent, the rate at which the therapeutic agent is released from the device, the rate-controlling membrane being substantially free of therapeutic agent prior to placement of the device onto the skin or mucosa. When the device is placed on the skin or mucosa, water is absorbed from the skin or mucosa through the rate-controlling membrane and into the reservoir. The system becomes hydrated as a result of the absorbed water and thereby activates the activating agent, which aqueous solution of activating agent then promotes dissociation of the therapeutic agent from the ion-exchange resin. The delay of delivery is caused primarily by the time required for water from the skin to permeate through the rate-controlling membrane and into the reservoir to activate therapeutic agent displacement. The rate-controlling membrane controls the rate at which water is transported from the skin into the reservoir; the membrane thereby controls the delay time and indirectly controls the therapeutic agent release rate.

The present invention has the additional advantage of providing the therapeutic agent in a stable form prior to placement on the skin or mucosa as well as in a form suitable for absorption after such placement.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates in cross section a delivery device of the present invention.

FIG. 2 illustrates in cross section another delivery device of the present invention.

FIG. 3 illustrates in cross section yet another delivery device of the present invention.

FIG. 4 illustrates in cross section another delivery device of the present invention.

FIG. 5 is a graph showing the release rate vs. time for nicotine devices of Examples 1 through 6.

FIG. 6 is a graph showing the release rate vs. time for nicotine from a device of Example 8, both newly prepared and after 13 months' storage, in comparison with a prior art nicotine transdermal delivery device.

FIG. 7 is a graph showing the release rate vs. time for nicotine from devices of Example 10, both newly prepared and after 8 weeks' storage at different temperatures.

FIG. 8 is a graph showing the release rate vs. time for nicotine from devices of Example 12.

DETAILED DESCRIPTION OF THE INVENTION AND OF THE PREFERRED EMBODIMENTS

Therapeutic agents suitable for transdermal administration exist in various forms, some of which are more suitable for stable storage and some of which are more suitable for administration through skin or mucosa.

According to this invention, a therapeutic agent delivery device is provided in which the therapeutic agent is present in the administration-suitable, but often unstable form in such manner that it is also stable in the device. This is accomplished by complexing the therapeutic agent with an ion-exchange resin. The therapeutic

agent/ion-exchange complex forms a matrix that is stable at high temperature and over an extended period of time. There is no evaporation, migration or solubilization. It is, in fact, so stable that agent cannot be released at a therapeutic rate from the delivery device into the skin unless and until it is freed by another cation or anion, depending on the nature of the agent, or by neutralization of the ionic form of the drug under moist conditions.

Neutralization and release of the therapeutic agent is provided in the present invention by the presence of an acid or base activating agent together with the therapeutic agent/ion-exchange resin complex. In the absence of water, this activating agent will not react with the complex. However, in the presence of water which has been absorbed from the skin or mucosa, the activating agent forms a solution and promotes the dissociation of the therapeutic agent and the resin, making the therapeutic agent available for delivery from the device.

Any nontoxic pharmaceutical grade ion-exchange resin used to bind cationic or anionic agent molecules at the ion exchange sites may be employed in this invention. For example, any wide range of cationic (for basic pharmacological agents) or anionic (for acidic agents) ion exchange resins can be employed. Examples of cationic resins would be weak acid cation exchange resins with the functional moiety being a carboxylic acid (-COOH) group. This could be derived from polymers or copolymers such as methacrylic acid or polymethacrylate. A strongly acidic cation exchange resin having the functional group $-SO_3Na$ derived from the polymer styrene could also be employed. Examples of anionic resins are those having the functional group $NH.NH_2$ which are weakly basic and could be derived from phenolic polyamines, or the strongly basic type having as the functional group $-N(R_3)$, also derived from polystyrenes.

Ion exchange resins are well known in the art, and the present invention encompasses all ion exchange resins. The ion exchange resins discussed above are known in the art as the amberlite class, such as, for example, Amberlite® IR-120, Amberlite® IRP-69, Amberlite® IRP-64, Amberlite® IRP-58, or Amberlite® IRC-50.

It is believed that this invention has utility in connection with the delivery of any ionizable drug within the broad class normally delivered through body surfaces and membranes, including skin and mucosa. As used herein, the expressions "drug", "active agent" and "therapeutic agent" are used interchangeably and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, those disclosed in U.S. Pat. Nos. 3,598,122, 3,598,123, 4,286,592, 4,314,557, 4,379,454 and 4,568,343, all of which are incorporated herein by reference.

This invention has particular utility in connection with the delivery of drugs that are very unstable in their neutral acid or base form (also referred to herein as their "active form") . It is also useful for those drugs that are too soluble in their active form in delivery devices to maintain the system's integrity during shelf life; that is, they tend to degrade one or more of the components of the system, including the adhesive, upon prolonged exposure such as is the case under storage conditions. This invention also eliminates the initial burst of drug from the device. This is particularly beneficial in delivering drugs that have a tendency in large doses to irritate the skin. Additionally, the present invention is particularly useful in delivering those drugs which should not be delivered in a continuous manner over a prolonged period of time, such as drugs that, through continuous administration, become addictive or develop a tolerance in the host. Other agents which may be beneficially delivered according to this invention include drugs where a therapeutic effect is desired at an inconvenient time or where no therapeutic effect is desired for a particular initial time period.

Agents may be selected from hypnotics, opioids, analgesics, anti-inflammatories, nonsteroidal anti-inflammatories, anticholinergics, hormones, hydrogen antagonists, antiparkinsonian agents, vitamins, nutrients, antiangina agents, stimulants, depressants, antihypertensives, and the like. Particular drugs which may be employed with the present invention include, but are not

limited to, peptides and proteins, cimetidine, pseudoephedrine, ephedrine, chlorpheniramine, oxybutynin, dextromethorphan, phenylpropanolamine, phenylephrine, propylhexedrine, nicotine, nitroglycerin, amyl nitrate, propranolol, timolol, atenolol, terbutaline, salbutamol, ergonovine, ergotamine, melatonin, caffeine, aspirin, indomethacin, acetaminophen, para-aminosalicylic acid, fentanyl, sufentanyl, scopolamine, secoverine, benztropine, naprosin, isosulfide mononitrate, isosulfide dinitrate, nicorandil, and the like.

One drug which is particularly suitable for delayed delivery according to the present invention is nicotine. Transdermal delivery devices for the immediate delivery of nicotine have been recently introduced for the treatment of smoking cessation. These devices are available for delivery over 24 hours, where the patient replaces the device once every 24 hours, and for delivery over 12 hours, where the patient may either replace the device once every 12 hours or wear a device for a 12-hour period, followed by no device for 12 hours. Each of these regimens can provide drawbacks. With delivery of nicotine continuously over 24 hours (with either the 24-hour patch or two 12-hour patches), certain side effects have been reported that are associated with delivery of nicotine during sleeping hours. These include abnormal dreams and insomnia. If a device is not worn during sleep in order to reduce or eliminate these side effects, then a new nicotine patch would not be applied until after awakening in the morning. However, when no nicotine has been delivered during the night, the plasma nicotine concentrations will be low and smokers encounter early morning withdrawal symptoms such as "morning craving" and the urge to smoke. Placement of a nicotine patch after awakening will not immediately relieve these cravings, and this could greatly decrease the efficacy of the transdermal devices for stopping the smoking habit.

A delayed delivery device of the present invention can be designed to be placed on the skin at dinner time or at bedtime, for example, and would not begin delivery of nicotine to the skin until shortly prior to awakening, such as one to three hours prior to awakening, usually five to eight hours after initial placement, after which time therapeutic levels of nicotine would be delivered for

about the next sixteen to nineteen hours. This initial delay of nicotine delivery could reduce or eliminate the side effects of abnormal dreams and insomnia because significant drug delivery will only occur during waking hours. At the same time, efficacy will be maintained because plasma nicotine concentrations will be achieved in sufficient time prior to awakening to overcome any morning craving and the urge to smoke.

Other drugs which are particularly suited for delayed delivery according to the present invention include the nonsteroidal anti-inflammatories for morning stiffness of joints; short-acting hypnotics for insomnia; oxybutynin for incontinence; isosorbide mononitrate, isosorbide dinitrate and nicorandil for antiangina; and melatonin for jet lag, sleeping disorders, and the like.

Adsorption of drugs onto ion exchange resins is well known to the art, as is disclosed in, for example, U.S. Pat. Nos. 2,990,332 and 4,221,778, the disclosures of which are incorporated herein by reference.

The activating agent which is present in the drug reservoir together with the drug/resin complex is anhydrous and can be either an acid or a base, depending on the nature of the particular therapeutic agent. Suitable acids include, but are not limited to, citric acid, succinic acid, oxalic acid, succinic anhydride, phthalic acid, phthalic anhydride, sodium bisulfate and salicylic acid. Suitable bases include, but are not limited to, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, monobasic sodium phosphate, dibasic sodium phosphate, sodium oxalate, sodium succinate, sodium citrate, sodium salicylate, and all other salts of organic acids.

Any organic or inorganic salt containing the appropriate counter ion for the ion exchange resin can be employed according to this invention.

In a preferred embodiment of this invention, a therapeutic agent is transdermally administered to the skin or mucosa from a diffusional delivery device, the agent being stored in the delivery device in complexation with an ion-exchange resin. The therapeutic agent is dissociated from the ion-exchange resin during delivery from the device by reaction with an activating agent which has formed a

solution with water supplied by the body. While the dissociated therapeutic agent is able to permeate the layers of the delivery device and ultimately the skin itself, the complexed therapeutic agent cannot. The inability of the therapeutic agent in its complexed form to permeate the system and the skin ensures that the therapeutic agent will remain within the reservoir until the onset of delivery is desired.

In order that premature reaction be prevented, the agent/resin complex and the activating agent are maintained in an anhydrous environment prior to use. Within these broad limitations, the specific structure of the delivery device is not critical to this invention. The therapeutic agent/ion-exchange resin complex and the activating agent may be dispersed within an anhydrous or hydrophobic matrix, either as a solid, non-aqueous liquid or gel, or mixed with suitable anhydrous or hydrophobic carriers, permeation enhancers and the like as is known in the art. The matrix or carrier and other excipients must be chosen from those which do not solubilize the activating agent. Materials which may be suitable as matrices and carriers include, but are not limited to, ethylene vinyl acetate copolymers (preferably having from 9 wt% to 60 wt% vinyl content), silicone oil, mineral oil, sesame oil, olive oil, and polybutene. Other materials are known to the art or may be determined without undue experimentation. The devices are preferably in the form of an adhesive patch or the like but can also be in the form suitable for application to the skin or mucosa such as an anhydrous ointment, gel or matrix, for example. If desired, means for controlling the release rate of the therapeutic agent can also be used, as is known in the art.

In accordance with a preferred embodiment of the invention, the activating agent is activated by water which is readily available from the site of administration, such as the cutaneous surface, particularly in occluded skin regions. The delivery devices of the present invention include a rate-controlling membrane between the drug-releasing surface of the reservoir and the skin or mucosa for controlling the rate at which water from the skin or mucosa is taken up into the reservoir, which in turn controls the rate of dissolution of the activating agent. The delay of delivery of active agent or

drug from the device is caused primarily by the time required for water to permeate through the rate-controlling membrane and into the reservoir to activate drug displacement. The rate-controlling membrane thereby controls the delay time to onset of delivery of the drug from the device.

The rate-controlling membrane may be fabricated from permeable, semipermeable or microporous materials which are known to the art to control the rates of agents or fluids into and out of delivery devices. Materials suitable for use as the water-uptake rate-controlling membrane include, but are not limited to, polyolefins such as polyethylene, polypropylene, polyester, polycarbonate, and the like; and copolymers such as polystyrene-butadiene copolymer, ethylene vinyl acetate copolymer, ethylene acrylic acid copolymer, ethylene ethylacrylate copolymer, ethylene methylacrylate copolymer, copolyester elastomers of tetramethylene terephthalate and poly(tetramethylene ether)glycol terephthalate (Hytrel®), and the like. The length of the delay period can be controlled by the choice of material used as the rate-controlling membrane, by the thickness of the membrane, or by a combination of these.

Referring now to the Figures, which are not drawn to scale but are presented for purposes of illustration, FIG. 1 shows transdermal delivery device 10 which includes a drug-impermeable backing layer 102, an anhydrous reservoir 104 containing a drug in complexation with an ion-exchange resin and also an activating agent admixed with the complex, and a rate-controlling membrane 106. Backing layer 102 and rate-controlling membrane 106 are sealed together at their edges, preferably by means of a heat seal, to form a sealed pouch for containing reservoir 104.

When maintained in contact with a wearer's skin by an adhesive overlay or a belt, buckle or elastic band (not shown), for example, water from the skin will begin to penetrate rate-controlling membrane 106 and to be absorbed into reservoir 104, where it forms a solution with the activating agent. The solubilized activating agent then reacts with the drug/ion exchange resin complex to dissociate the drug from the resin, freeing the drug to then pass through rate-controlling membrane 106 and into the skin.

Backing support layer 102 is not permeable to the active agent. Appropriate materials are known to the art, representative examples of which are listed in the patents previously incorporated herein by reference. Reservoir 104 is an anhydrous environment for containing the drug/resin complex and the activating agent prior to placement on the skin. Reservoir 104 may also contain stabilizing agents, thickeners, permeation enhancers or other additives as are known to the transdermal delivery art. Rate-controlling membrane 106 is preferably substantially free of dissolved active agent or drug.

As used herein, the term "substantially free of active agent" means either free of agent or containing an amount of active agent or drug insufficient to establish and maintain therapeutically effective active agent delivery rates at the time of application to the delivery site.

As used herein, the term "therapeutically effective" rate or amount refers to a rate or amount of active agent that provides a therapeutic or beneficial result or effect.

Device 10A, shown in FIG. 2, in addition to backing layer 102, reservoir 104 and rate-controlling membrane 106, has adhesive layer 108 on the skin-contacting surface of the device for maintaining the device on the skin. Silicone compounds are commonly used as adhesives for the contact adhesive layer 108; however, numerous materials are known to the art which possess the requisite strength and skin compatibility, examples of which are given in the patents previously incorporated herein by reference. Also present is a removable release liner 110 on the skin-contacting surface of adhesive layer 108, which liner is removed prior to placement of the device on the skin or mucosa. Such release liners are known to the art and are typically of siliconized paper or siliconized polymer or the like.

FIG. 3 illustrates a laminated device 100 according to this invention. This device is not end-sealed. Device 100 has a drug-impermeable backing layer 102, a reservoir lamina layer 104a containing the drug/ion-exchange resin complex and the activating agent, a rate-controlling membrane 106a and an in-line contact adhesive layer 108. Device 100 may also include a removable release liner (not shown) adjacent to adhesive layer 108. Reservoir

lamina 104a may, in addition to permeation enhancers and stabilizing agents for example, contain anhydrous or hydrophobic rheological modifiers, viscosity boosters or thixotropic/gelling agents to prevent flow of the drug matrix beyond the device confines. Rate-controlling membrane 106a does not flow, as this membrane, generally, has a rigidity when dry and, when moistened, it will continue to retain its integrity.

Device 200, illustrated in FIG. 4, is similar to device 100 of FIG. 3, except that device 200 has an anhydrous reservoir 104b comprising two lamina layers, a first layer 112 which contains the activating agent and a second layer 114 which contains the drug/ion-exchange resin complex. Activating agent layer 112 may be positioned either between drug/resin complex layer 114 and rate-controlling membrane 106a, as illustrated in FIG. 4, or between complex layer 114 and backing layer 102 (not shown). As fluid enters device 200 through the rate-controlling membrane, the activating agent becomes activated and the resulting aqueous solution of activating agent migrates from layer 112 into layer 114 to promote dissociation of the drug from the ion-exchange resin, making the drug available for delivery from the device.

Having thus generally described the present invention, the following specific examples of the invention are provided.

EXAMPLE 1

Transdermal delayed delivery devices for the delayed onset of delivery of nicotine according to the present invention and generally as illustrated in FIG. 3 were prepared as follows.

A cation exchange resin having a $-SO_3H$ functional group (Amberlite® IRP-69, the sodium form; Aldrich Chemicals) was immersed in 5 volumes of 2 N HCl solution and stored overnight. The swollen resin was washed on a sintered glass filter with 10 volumes of 0.5 N HCl and then 10 volumes of distilled water. The acidic resin was dried under vacuum at 50°C overnight.

Twenty grams of the dried acidified cation exchange resin was mixed with 20 g of nicotine base. Two volumes (80 g) of water were added and the mixture was stirred well. The pH of the resin slurry was adjusted to 5. The slurry was then filtered on a sintered glass

filter and washed well with water. The wet resin was dried under vacuum at 50°C overnight. An analysis of nicotine complexed to the resin showed that 0.49 mg of nicotine was bound to every milligram of the drug/acidified resin complex.

To prepare the device, 37.5% of the nicotine/resin complex, 12.5% of micronized sodium carbonate (the activating agent), and 50.0% ethylene vinyl acetate copolymer having a 40% vinyl content (EVA40) were melt-blended together on a hot plate or in a mill or mixing machine, and the formulation was then melt-pressed to a 15 mil (0.38 mm) film to form the nicotine reservoir layer. The reservoir layer was then laminated to a backing layer of pigmented Medpar® (a trilaminate of pigmented medium density polyethylene/aluminum-polyethyleneterephthalate/low density polyethylene; 3M). A 1.5 mil (0.038 mm) layer of Hytrel® 4056 (33% tetramethylene terephthalate/67% poly(tetramethylene ether)glycol-terephthalate; the rate-controlling membrane) was then laminated onto the opposite surface of the reservoir layer. Silicone adhesive 355 containing 13% silicone medical fluid 100cs was cast onto FCD/polyester 1022 release liner to give the adhesive layer, and the exposed side of the adhesive layer was then laminated onto the bottom side on the rate-controlling membrane and the device cut to a desired size/shape to give the final nicotine delayed onset delivery device ("System Type I").

EXAMPLE 2

Transdermal delayed delivery devices for the delayed onset of delivery of nicotine according to the present invention and generally as illustrated in FIG. 2 were prepared as follows.

To prepare the delivery device, 37.5% of the nicotine/resin complex (from Example 1) was mixed together under anhydrous conditions with 12.5% micronized sodium carbonate (the activating agent) and 50.0% polyethylene glycol with a molecular weight of 400 (PEG 400) to form a reservoir matrix. An amount of 400 mg of the reservoir formulation was heat-sealed between Hytrel® 4056 (1.5 mil, 0.038 mm; the rate-controlling membrane) and a backing membrane (made by casting Hytrel® 4056 onto 1 mil, 0.025 mm, polyester) to give a 10 cm^2 device. Silicone adhesive 355 containing 13% silicone medical

fluid 100cs was cast onto FCD/polyester 1022 release liner to give the adhesive layer, and the exposed side of the adhesive layer was then laminated onto the bottom side of the device on the rate-controlling membrane and the device cut to the desired size/shape to give the final nicotine delayed onset delivery device ("System Type II").

EXAMPLE 3

Nicotine-containing devices were prepared which were identical to those in Example 2, except that the drug reservoir was composed of 60% nicotine/resin complex, 20% micronized sodium carbonate and 20% micronized sorbitol as a dry powder. Loading of the powder was 250 mg for a 10 cm^2 device ("System Type III").

EXAMPLE 4

Nicotine-containing devices were prepared which were identical to those in Example 3, except that the drug reservoir was composed of 75% nicotine/resin complex and 25% micronized sodium carbonate as a dry powder. Loading of the powder was 200 mg for a 10 cm^2 device ("System Type IV").

EXAMPLE 5

Nicotine-containing devices were prepared which were identical to those in Example 2, except that the drug reservoir was composed of 50% nicotine/resin complex and 50% PEG 400. The reservoir did not contain sodium carbonate. A 10 cm^2 device contained 400 mg of the reservoir formulation ("System Type V").

EXAMPLE 6

Nicotine-containing devices were prepared which were identical to those in Example 4, except that the drug reservoir was composed of 100% nicotine/resin complex as a dry powder. The reservoir did not contain sodium carbonate. Loading of the powder was 200 mg for a 10 cm^2 device ("System Type VI").

EXAMPLE 7

The devices of Examples 1 through 6 were tested in vitro for nicotine release. Release rates of nicotine over time through a 1.5 mil (0.038 mm) Hytrel® membrane into an aqueous bath at 35°C were determined, the Hytrel membrane being used because it simulates the water transport properties of human skin. For the test, the release liner was removed from each device, or system, and each device was covered at its drug release surface with the Hytrel membrane to control water availability to the test system in all release rate tests. Each test was run over 24 hours at 35°C. The release medium was distilled water. Drug concentration was determined by UV absorption at 259 nm.

The results are presented in FIG. 5, which shows the release rate profile of each type of system. System types I, III and IV all exhibited an initial delay prior to release of nicotine. System II had a higher initial release rate due to the partial solubilization of sodium carbonate in PEG 400. System types V and VI did not contain the sodium carbonate activating agent and, as can be seen, they did not release any detectable nicotine.

EXAMPLE 8

Nicotine-containing delivery devices similar to those of Example 2 were prepared, except that the reservoir contained 20% nicotine/resin complex (where the ion exchange resin is cation exchange resin Amberlite® IRP-64, with sulfonic acid functionality, sodium form acidified to $-SO_3H$ prior to binding with nicotine), 6% sodium carbonate and 74% silicone fluid, and the backing was composed of a 1.5 mil (0.038 mm) polyester/1.8 mil (0.046 mm) Hytrel® 4056 laminate. Additionally, the thickness of the Hytrel rate-controlling membrane was 1.8 mil (0.046 mm).

The stability of the above devices after prolonged storage was determined as follows. The devices were stored in a sealed pouch for 13 months at 30°C. They were then tested for their release rate through a Hytrel membrane, following the procedures of Example 7, in comparison with newly prepared devices and also in comparison with a prior art device (the Nicoderm® transdermal patch, identified as "Clinical System" in FIG. 6). The results are shown in FIG. 6, which

indicates that the devices of the present invention not only have a delayed onset of delivery of nicotine, but also that the nicotine/resin complex provides excellent drug stability in the device, even after prolonged storage at elevated temperature.

EXAMPLE 9

A benztropine delivery device is prepared as follows.

Ten grams of dried acidified cation exchange resin (Amberlite® IRP-69) is mixed with 15 g of benztropine base in 100 mL of water. The mixture is stirred well, and the pH of the resin slurry is adjusted to 5. The slurry is then filtered on a sintered glass filter and washed well with water. The wet resin is dried under vacuum at 50°C overnight. An analysis of benztropine complexed with the resin shows that 0.54 mg of benztropine is bound to every milligram of the drug/resin complex.

To prepare the delivery device, 20 wt% of the benztropine/resin complex is mixed together under anhydrous conditions with 5 wt% of micronized sodium carbonate (the activating agent) and 75 wt% of polybutene (a mixture of 68 parts of PB L-100 and 55 parts of PB H-350) to form a reservoir matrix. An amount of 400 mg of the reservoir formulation is heat-sealed between a rate-controlling membrane layer of EVA 33 (2 mils, 0.05 mm; EVA having 33% vinyl acetate content) and a backing layer of pigmented Medpar®. Acrylic adhesive (MSP041991P, 3M) is then laminated onto the rate-controlling membrane to give the final ion exchange resin/benztropine complex delivery device.

EXAMPLE 10

A nicotine-containing delivery device was prepared as follows, generally according to the procedures of Example 1.

A mixture of 52% of nicotine/resin complex (prepared as in Example 1 and having 37.8% nicotine content), 18% of micronized anhydrous sodium carbonate (the activating agent) and 30% ethylene vinyl acetate copolymer having a 28% vinyl acetate content (EVA28; ELVAX® 210, from DuPont) was blended together using a dispersion mixer. The formulation was then extruded to a 4 mil (0.10mm) film to form the nicotine reservoir. The reservoir layer was then laminated

to a backing layer of pigmented Medpar®. A 1 mil (0.025mm) layer of EVA40 was then laminated to the opposite surface of the drug reservoir layer to provide a rate controlling membrane. Acrylic adhesive (MSP041991P, from 3M) was laminated onto the bottom side of the device on the rate controlling membrane to give the final nicotine delay onset delivery device.

The release rate of nicotine from devices prepared according to this example, both those devices freshly made and those which had been stored at either 4°C, room temperature or 30° C for eight weeks, was tested following the procedures of Example 7, except that the Hytrel® 4056 test membrane was 5 mil (0.13mm) thick. The test results are presented in FIG. 7, which shows the release rate profile of both the newly prepared devices (solid circle) and the stored devices (clear triangle = 4°C; solid triangle = RT; square = 30°C).

EXAMPLE 11

The effect of the relative amount of activating agent on the release rate of a drug from devices according to the invention was evaluated as follows.

Nicotine-containing transdermal delayed-delivery devices according to the invention and generally as illustrated in FIG. 2 were prepared following the procedures of Example 2. The devices consisted of a Hytrel 4056 rate-controlling membrane (1.5 mil; 0.038 mm), contact adhesive layer of silicone adhesive 355 containing 13% silicone medical fluid 100 cs, and a drug reservoir having nicotine/resin complex (with 37.6% nicotine payload), 21.4 mg/10 cm^2 and micronized sodium carbonate (as the activating agent). The mole ratio of sodium carbonate to nicotine was either 0.347, 0.495, 0.693, 0.851, 1.040 or 1.386.

The release rate of nicotine from the devices at 35°C was tested following the procedures of Example 7. The results showed that the release rate and 24 hour cumulative drug released increased linearly with the increasing mole ratio of sodium carbonate to nicotine. The rate, however, leveled off at the ratio of 0.851.

EXAMPLE 12

The effect of the particle size of sodium carbonate on the release rate of a drug from devices having a solid drug reservoir matrix was evaluated as follows.

A nicotine-containing delivery device was prepared as follows, generally according to the procedures of Example 1. A mixture of 48% of nicotine/resin complex (prepared as in Example 1 and having 31.2% nicotine content), 12% of anhydrous sodium carbonate (the activating agent) and 40% ethylene vinyl acetate copolymer having a 40% vinyl acetate content (EVA40) was blended together using a dispersion mixer. The particle size of the sodium carbonate was varied in different formulations. The formulation was then extruded to a 5 mil (0.125mm) film to form the nicotine reservoir. The reservoir layer was then laminated to a backing layer of pigmented Medpar®. A 2 mil (0.050mm) layer of EVA40 was then laminated to the opposite surface of the drug reservoir layer to provide a rate controlling membrane. Acrylic adhesive (MSP041991P, from 3M) was laminated (1 mil, 0.025mm) onto the bottom side of the device on the rate controlling membrane and the device cut to a desired size/shape to give the final nicotine delay onset delivery device.

The release rate of nicotine from devices prepared according to this example was tested following the procedures of Example 7, except that the Hytrel® 4056 test membrane was 5 mil (0.13mm) thick. The test results are presented in FIG. 8 (particle sizes of sodium carbonate are indicated on the Figure).

While this invention has been described with respect to certain specific embodiments thereof, it should not be construed as being limited thereto. Numerous modifications and substitutions will suggest themselves to workers skilled in the art and may be made without departing from the scope of this invention, which is limited only by the following claims.

WHAT IS CLAIMED IS:

1. A nonaqueous composition comprising:

a therapeutically effective amount of a therapeutic agent in complexation with an ion exchange resin, and

an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for said therapeutic agent.

2. A composition according to claim 1 wherein said therapeutic agent is nicotine.

3. A composition according to claim 2 wherein said ion exchange resin is a sulfonic acid resin.

4. A composition according to claim 3 wherein said activating agent is selected from sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and dibasic sodium phosphate.

5. A composition according to claim 1 which further comprises a carrier, which carrier does not solubilize said activating agent.

6. A composition according to claim 5 wherein said carrier is selected from ethylene vinyl acetate copolymer, silicone oil, sesame oil, olive oil and polybutene.

7. A delivery device for the percutaneous administration of a therapeutic agent to skin or mucosa and adapted to delay the onset of therapeutic agent delivery at a therapeutically effective rate for a predetermined time after placement of said device in therapeutic agent-transmitting relationship to the skin or mucosa, said device comprising, in combination:

a backing layer impermeable to said therapeutic agent;

a nonaqueous reservoir which comprises a) said therapeutic agent in a therapeutically effective amount in

complexation with an ion exchange resin and b) an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for said therapeutic agent, said reservoir having a surface through which said therapeutic agent is released to the skin or mucosa;

a rate-controlling membrane disposed between the skin or mucosa and said releasing surface of said reservoir for controlling the rate at which water is absorbed into said reservoir, said rate-controlling membrane being substantially free of dissolved therapeutic agent prior to placement of said device onto the skin or mucosa; and

means for maintaining said device in therapeutic agent-transmitting relationship to the skin or mucosa.

8. A device according to claim 7 wherein said rate-controlling membrane is selected from ethylene vinyl acetate copolymer, ethylene acrylic acid copolymer, ethylene ethylacrylate copolymer, ethylene methylacrylate copolymer, and copolyester elastomers of tetramethylene terephthalate and poly(tetramethylene ether)glycol terephthalate.

9. A device according to claim 7 wherein said activating agent is selected from sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and dibasic sodium phosphate.

10. A device according to claim 7 wherein said therapeutic agent is nicotine.

11. A device according to claim 10 wherein said ion exchange resin is a sulfonic acid resin.

12. A device according to claim 11 wherein said activating agent is sodium carbonate and said rate-controlling membrane is selected from the group consisting of a copolyester elastomer of tetramethylene terephthalate and poly(tetramethylene ether)glycol terephthalate and a copolymer of ethylene vinyl acetate.

13. A device according to claim 7 wherein said means for maintaining said device to the skin or mucosa comprises a contact adhesive disposed between said rate-controlling membrane and the skin or mucosa.

14. A device according to claim 13 wherein the total loading of therapeutic agent in said contact adhesive at the time of application to the skin or mucosa is insufficient to establish and maintain therapeutic agent delivery at a therapeutic rate.

15. A device according to claim 12 wherein said means for maintaining said device to the skin or mucosa comprises a contact adhesive disposed between said rate-controlling membrane and the skin or mucosa.

16. A device according to claim 15 wherein the total loading of therapeutic agent in said contact adhesive at the time of application to the skin or mucosa is insufficient to establish and maintain therapeutic agent delivery at a therapeutic rate.

17. A device according to claim 7 wherein said reservoir further comprises a carrier, which carrier does not solubilize said activating agent.

18. A device according to claim 17 wherein said carrier is selected from ethylene vinyl acetate copolymer, silicone oil, sesame oil, olive oil and polybutene.

19. A method for delaying delivery of a therapeutic agent to the skin or mucosa, said method comprising the steps of:

1) placing a nonaqueous composition onto the skin or mucosa, said composition comprising:

a therapeutically effective amount of a therapeutic agent in complexation with an ion exchange resin, and

an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for said therapeutic agent;

2) allowing water from the skin or mucosa to be absorbed into said composition; and

3) allowing said activating agent to form a solution with said water, said activating agent in solution reacting to dissociate said therapeutic agent from said ion exchange resin, the dissociated therapeutic agent being neutralized and able to permeate into the skin.

20. A method for delaying delivery of a therapeutic agent to the skin or mucosa, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa, said device comprising:

a backing layer impermeable to said therapeutic agent;

a nonaqueous reservoir which comprises a) said therapeutic agent in a therapeutically effective amount in complexation with an ion exchange resin and b) an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for said therapeutic agent, said reservoir having a surface through which said therapeutic agent is released to the skin or mucosa;

a rate-controlling membrane disposed between the skin or mucosa and said releasing surface of said reservoir for controlling the rate at which water is absorbed into said reservoir, said rate-controlling membrane being substantially free of dissolved therapeutic agent prior to placement of said device onto the skin or mucosa; and

means for maintaining said device in therapeutic agent-transmitting relationship to the skin or mucosa;

2) allowing water from the skin or mucosa to be absorbed into said reservoir through said rate-controlling membrane; and

3) allowing said activating agent to form a solution with said water, said activating agent in solution reacting to dissociate said therapeutic agent from said ion exchange resin,

the dissociated therapeutic agent being neutralized and able to permeate out of said device.

21. A method for reducing the side effects associated with the transdermal delivery of nicotine during sleeping hours, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa prior to bedtime, said device comprising:

a backing layer impermeable to nicotine;

a nonaqueous reservoir which comprises a) nicotine in a therapeutically effective amount in complexation with an ion exchange resin and b) an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for nicotine, said reservoir having a surface through which nicotine is released to the skin or mucosa;

a rate-controlling membrane disposed between the skin or mucosa and said releasing surface of said reservoir for controlling the rate at which water is absorbed into said reservoir, said rate-controlling membrane being substantially free of dissolved nicotine prior to placement of said device onto the skin or mucosa; and

means for maintaining said device in nicotine-transmitting relationship to the skin or mucosa;

2) allowing water from the skin or mucosa to be absorbed into said reservoir through said rate-controlling membrane; and

3) allowing said activating agent to form a solution with said water, said activating agent in solution reacting to dissociate nicotine from said ion exchange resin, the dissociated nicotine being neutralized and able to permeate out of said device at a time shortly prior to awakening.

22. A method for relieving the early morning withdrawal symptoms associated with low plasma concentrations of nicotine during sleeping hours, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa prior to bedtime, said device comprising:

a backing layer impermeable to nicotine;

a nonaqueous reservoir which comprises a) nicotine in a therapeutically effective amount in complexation with an ion exchange resin and b) an activating agent having a counter ion for said ion exchange resin and a neutralizing ion for nicotine, said reservoir having a surface through which nicotine is released to the skin or mucosa;

a rate-controlling membrane disposed between the skin or mucosa and said releasing surface of said reservoir for controlling the rate at which water is absorbed into said reservoir, said rate-controlling membrane being substantially free of dissolved nicotine prior to placement of said device onto the skin or mucosa; and

means for maintaining said device in nicotine-transmitting relationship to the skin or mucosa;

2) allowing water from the skin or mucosa to be absorbed into said reservoir through said rate-controlling membrane; and

3) allowing said activating agent to form a solution with said water, said activating agent in solution reacting to dissociate nicotine from said ion exchange resin, the dissociated nicotine being neutralized and able to permeate out of said device at a time shortly prior to awakening, whereby therapeutic plasma levels of nicotine are present at the time of awakening.

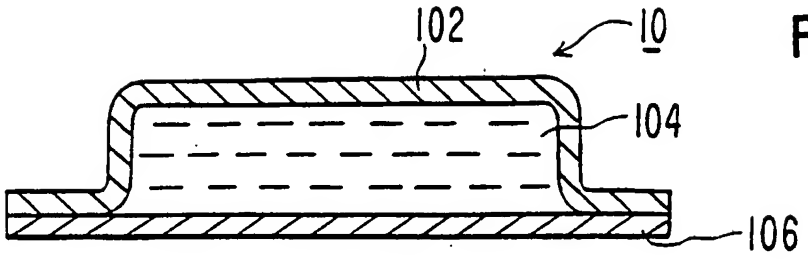


FIG. 1

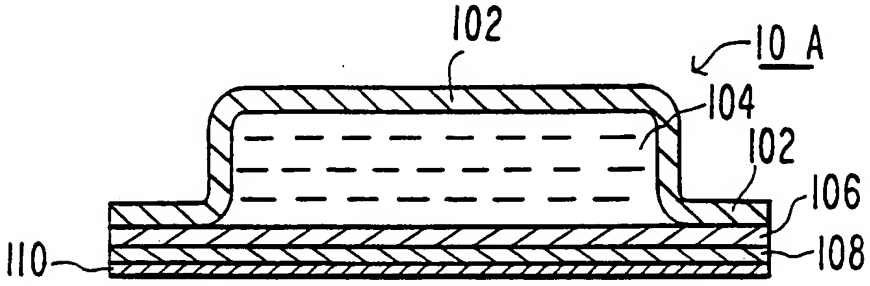


FIG. 2

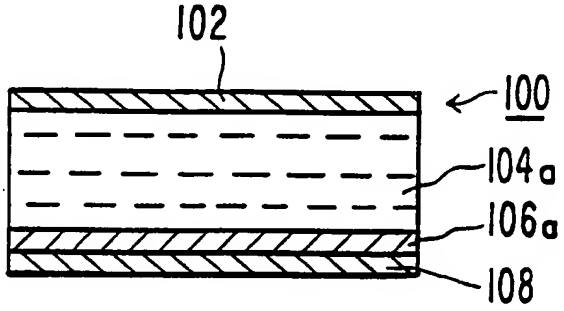


FIG. 3

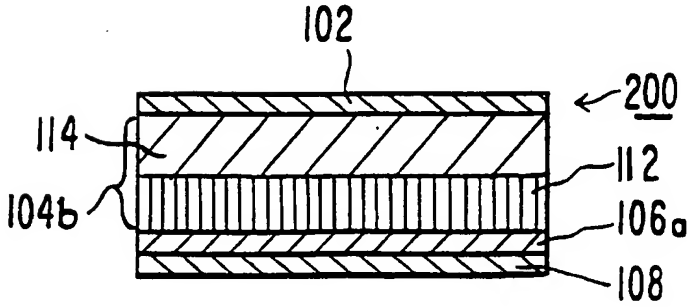


FIG. 4

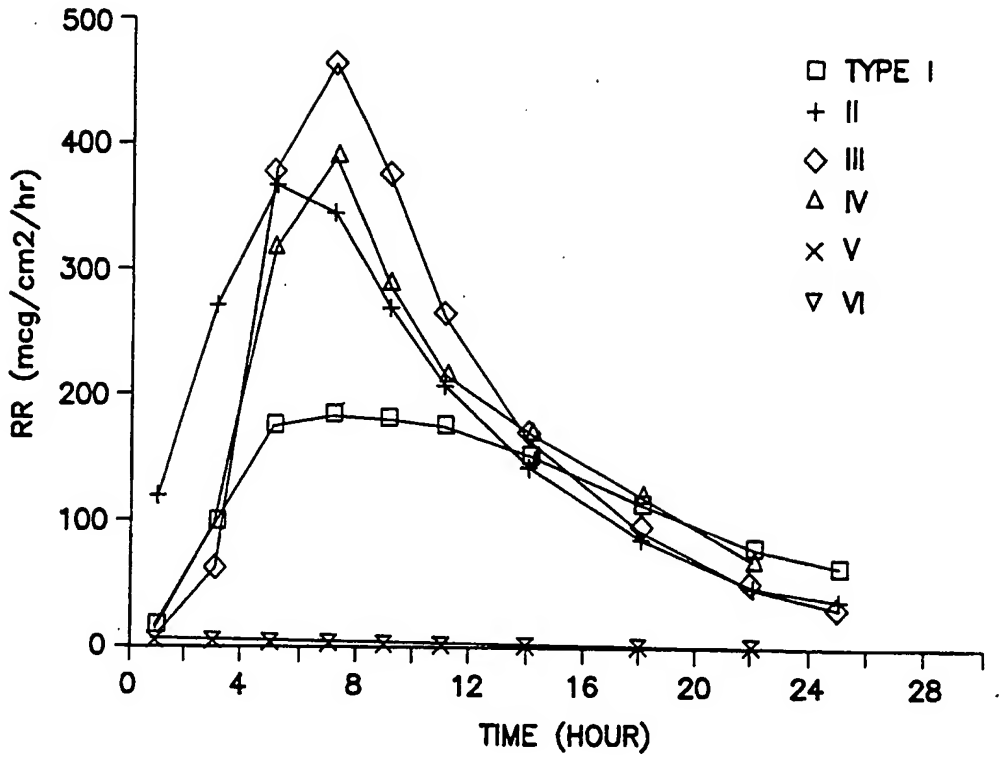
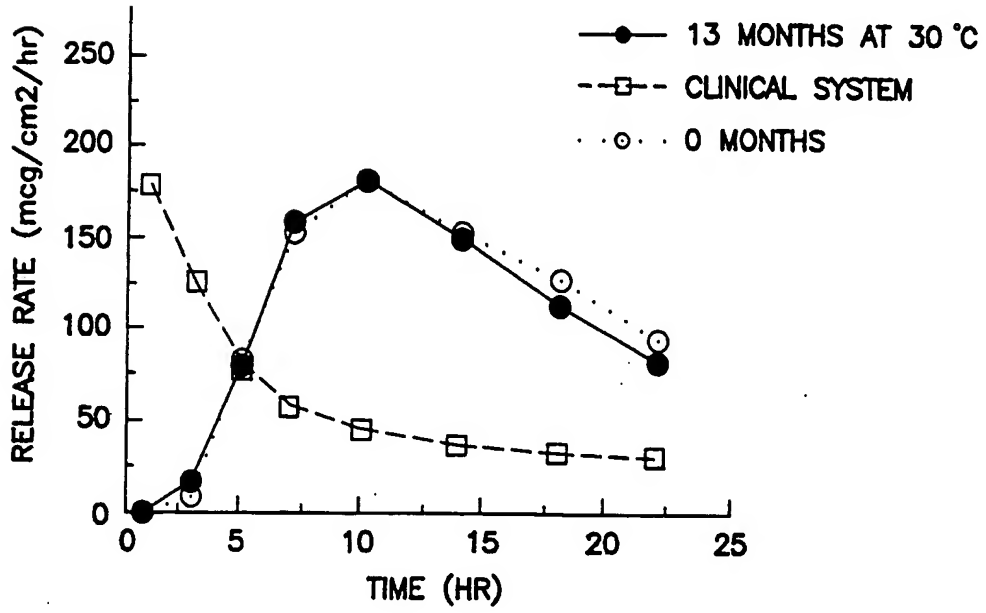

500
400
300
200
100
0
RR (mcg/cm2/hr)
0
4
8
12
16
20
24
28
TIME (HOUR)
TYPE I
II
III
IV
V
VI

FIG. 5


250
200
150
100
50
0
RELEASE RATE (mcg/cm2/hr)
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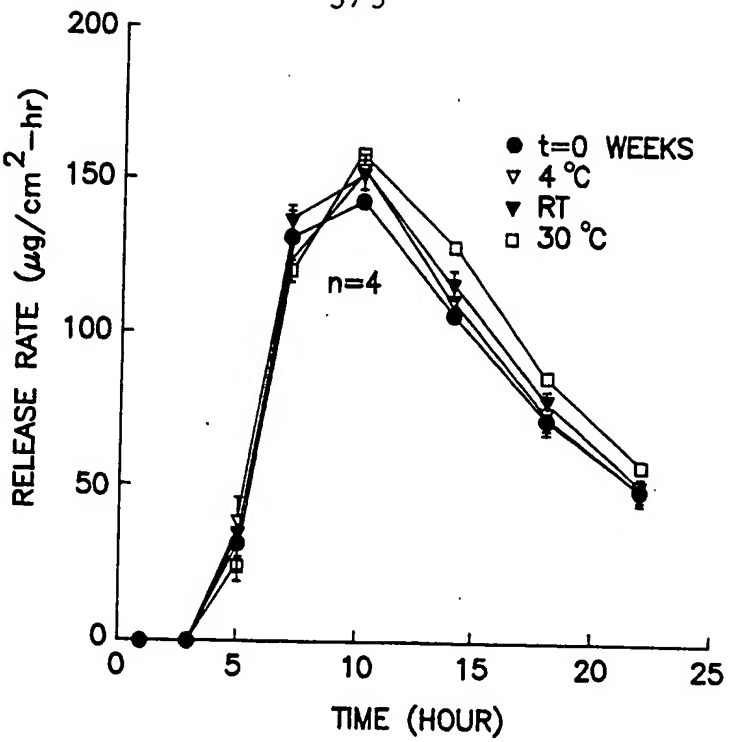
5
10
15
20
25
TIME (HR)
13 MONTHS AT 30 °C
CLINICAL SYSTEM
0 MONTHS

FIG. 6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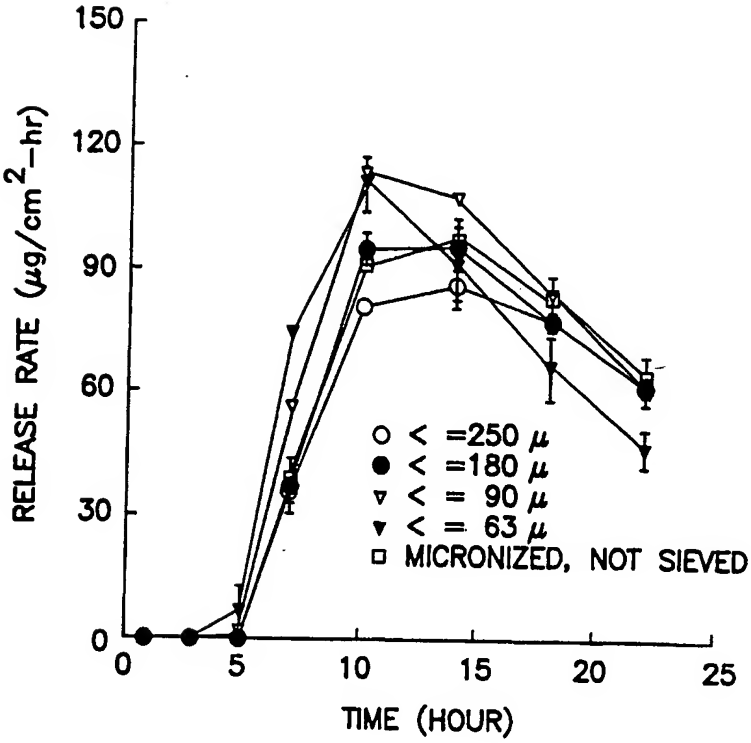
150
100
50
0
RELEASE RATE (μg/cm²-hr)
● t=0 WEEKS
▽ 4 °C
▼ RT
□ 30 °C
n=4
0
5
10
15
20
25
TIME (HOUR)

FIG. 7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120
90
60
30
0
RELEASE RATE (μg/cm²-hr)
○ < =250 μ
● < =180 μ
▽ < = 90 μ
▼ < = 63 μ
□ MICRONIZED, NOT SIEVED
0
5
10
15
20
25
TIME (HOUR)

FIG. 8

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 93/09637

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/70 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 195 643 (MENLEY & JAMES LABORATORIES LTD) 24 September 1986 cited in the application	1,3,4
Y	see page 1, line 5 - line 11 cited in the application see page 3, line 25 - page 4, line 7 see page 4, line 22 - line 26 see page 6, line 26 - line 36 see page 8; example 1 see claims 1-3	7-11, 13-18
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/US 93/09637

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 316 065 (ALZA CORPORATION) 17 May 1989 see page 4, line 23 - line 36 see page 5, line 21 - line 28 see page 6, line 6 - line 10 see page 6, line 55 see page 7, line 23 - line 25 see page 7, line 38 - line 47 see page 8 - page 9; example 2	7-11, 13-18
X	US,A,3 901 248 (LICHTNECKERT S. ET AL) 26 August 1975 see column 9, line 58 - line 62 see column 10, line 25 - line 30 see column 11; example 7 see claim 1	1-3
X	GB,A,1 349 207 (GALAT A.) 3 April 1974 see page 1, line 55 - line 67 see page 1, line 79 - page 2, line 27 see page 3	1,3,4
X	GB,A,1 462 356 (BEECHAM GROUP LTD) 12 July 1974 see page 4; table 2	1,3,4
A	US,A,4 650 484 (SHAW J. ET AL) 17 March 1987 see column 4, line 39 - line 55	12
A	EP,A,0 384 267 (LTS LOHMANN THERAPIE SYSTEME GMBH & CO.KG) 29 August 1990 see page 4 - page 5; example 1 see claims 1,12	7,9-11
A	WO,A,89 12470 (ALZA CORPORATION) 28 December 1989 see page 11 - page 12; example 1	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..ional Application No
PCT/US 93/09637

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0195643	24-09-86	US-A-	4692462	08-09-87
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		DE-A-	3881340	01-07-93
		JP-A-	1135717	29-05-89
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		GB-A-	1325011	01-08-73
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		EP-A-	0427741	22-05-91
		JP-T-	4500322	23-01-92
		US-A-	5004610	02-04-91